CLAIMS

We claim:

1. A method of developing a sensor cell for determining the activity of a target gene in said cell, comprising the steps of:

a. providing a homogeneous population of cells, wherein each of said cells comprises a signal transduction detection system,

b. introducing into said population of cells an isolated DNA construct comprising a promoter operatively linked to a targeting sequence, wherein:

i. said targeting sequence comprises a region of homology to said target gene sufficient to promote homologous recombination of said isolated DNA following introduction into said cells;

ii. said promoter is heterologous to said target gene;

iii. following said recombination said promoter controls transcription of an mRNA that encodes a polypeptide comprising an activatable domain; and

iv. said polypeptide is capable, upon activation of said activatable domain, of altering the signal detected from said signal transduction system,

c. incubating said population of cells under conditions which cause expression of said polypeptide;

d. incubating said population of cells under conditions which cause activation of said activatable domain of said polypeptide; and

e. selecting cells that have altered the signal detected from said signal transduction system.

2. The method according to claim 1, wherein:

a. said target gene encodes a polypeptide comprising a first modulator domain;

b. said isolated DNA construct further comprises a second modulator domain heterologous to said target gene, wherein said second modulator domain is positioned in said DNA

construct relative to said targeting sequence such that following homologous recombination said promoter controls the transcription on an mRNA that encodes a polypeptide comprising an activatable domain and said second modulator domain, but lacking said first modulator domain; and

c. upon activation of said activatable domain said modulator domain is capable of altering the signal detected from said signal transduction system.

3. The method according to claim 1 or 2, wherein said signal transduction detection system is selected from a reporter gene detection system, a transmembrane potential change detection system, a post-translational modification detection system and ion sensitive detection system.

4. The method according to claim 3, wherein said reporter gene detection system comprises a reporter gene selected from ß-lactamase, a naturally occurring *Aequorea victoria* green fluorescent protein, or a mutant *Aequorea victoria* green fluorescent protein.

5. The method according to claim 3, wherein said transmembrane potential change detection system is a FRET-based assay.

6. The method according to claim 3, wherein said ion sensitive detection system comprises an ion sensitive fluorophore selected from an UV light-excitable calcium indicator, a low affinity calcium indicator, a visible light-excitable calcium indicator, an UV light-excitable magnesium indicator, or a visible light-excitable magnesium indicator.

7. The method according to claim 2, wherein said second modulator domain comprises a zinc finger DNA binding domain.

8. The method according to claim 2, wherein said modulator domain comprises a DNA binding domain selected from a nuclear receptor DNA binding domain, a Gal4 DNA binding domain or a LexA DNA binding domain.

9. The method according to claim 1 or 2, wherein said target gene is selected from a nuclear receptor, a G-protein subunit, an ion channel subunit or a G-protein coupled receptor.

10. The method according to claim 1 or 2, wherein said isolated DNA construct further comprises a selectable marker gene.

11. A recombinant sensor cell comprising:

a. a signal transduction detection system; and

b. a promoter operatively linked to a DNA sequence that encodes a polypeptide comprising an activatable domain, wherein:

   i. said activatable domain is homologous to all or a portion of a polypeptide encoded by a target gene

   ii. said promoter is heterologous to said target gene; and

   iii. upon expression of said polypeptide and activation of said activatable domain the signal detected from said signal transduction detection system is altered.

12. The cell according to claim 11, wherein said polypeptide additionally comprises a modulator domain that is heterologous to said target gene, and wherein, upon expression of said polypeptide and activation of said activatable domain, said modulator domain causes the signal detected from said signal transduction system to be altered.

13. The cell according to claim 11 or 12, wherein said signal transduction detection system is selected from a reporter gene detection

system, a transmembrane potential change detection system, a post-translational modification detection system and ion sensitive detection system.

14. The cell according to claim 13, wherein said reporter gene detection system comprises a reporter gene selected from ß-lactamase, a naturally occurring *Aequorea victoria* green fluorescent protein, or a mutant *Aequorea victoria* green fluorescent protein.

15. The cell according to claim 13, wherein said transmembrane potential change detection system is a FRET-based assay.

16. The cell according to claim 13, wherein said ion sensitive detection system comprises an ion sensitive fluorophore selected from an UV light-excitable calcium indicator, a low affinity calcium indicator, a visible light-excitable calcium indicator, an UV light-excitable magnesium indicator, or a visible light-excitable magnesium indicator.

17. The cell according to claim 12, wherein said second modulator domain comprises a zinc finger DNA binding domain.

18. The cell according to claim 12, wherein said modulator domain comprises a DNA binding domain selected from a nuclear receptor DNA binding domain, a Gal4 DNA binding domain or a LexA DNA binding domain.

19. The cell according to claim 11 or 12, wherein said target gene is selected from a nuclear receptor, a G-protein subunit, an ion channel subunit or a G-protein coupled receptor.

20. The cell according to claim 11 or 12, further comprising a selectable marker gene.

21. A method of determining if a test compound is a modulator of a target gene or a target gene product comprising the steps of:

a. providing a recombinant sensor cell according to claim 3 or 4;

b. incubating said cell in the presence of a test compound under conditions which enable expression of said polypeptide;

c. incubating said cell under conditions which enable activation of said activatable domain of said polypeptide

d. measuring the signal detected from said signal transduction system in said cell.

22. The method according to claim 21, wherein said signal transduction detection system is selected from a reporter gene detection system, a transmembrane potential change detection system, a post-translational modification detection system and ion sensitive detection system.

23. The method according to claim 22, wherein said reporter gene detection system comprises a reporter gene selected from ß-lactamase, a naturally occurring *Aequorea victoria* green fluorescent protein, or a mutant *Aequorea victoria* green fluorescent protein.

24. The method according to claim 22, wherein said transmembrane potential change detection system is a FRET-based assay.

25. The method according to claim 22, wherein said ion sensitive detection system comprises an ion sensitive fluorophore selected from an UV light-excitable calcium indicator, a low affinity calcium indicator, a visible light-excitable calcium indicator, an UV light-excitable

magnesium indicator, or a visible light-excitable magnesium indicator.

26. The method according to claim 21, wherein said polypeptide comprises a zinc finger DNA binding domain that is heterologous to said target gene.

27. The method according to claim 21, wherein said polypeptide comprises DNA binding domain that is heterologous to said target gene and is selected from a nuclear receptor DNA binding domain, a Gal4 DNA binding domain or a LexA DNA binding domain.

28. The method according to claim 21, wherein said target gene is selected from a nuclear receptor, a G-protein subunit, an ion channel subunit or a G-protein coupled receptor.

29. A method of determining the activity of a target gene product comprising the steps of:

a. providing a recombinant sensor cell according to claim 3 or 4;
b. incubating said cell under conditions which enable expression of said polypeptide;
c. incubating said cell under conditions which enable activation of said activatable domain of said polypeptide
d. measuring the signal detected from said signal transduction system in said cell.

30. The method according to claim 29, wherein said signal transduction detection system is selected from a reporter gene detection system, a transmembrane potential change detection system, a post-translational modification detection system and ion sensitive detection

system.

31. The method according to claim 30, wherein said reporter gene detection system comprises a reporter gene selected from ß-lactamase, a naturally occurring *Aequorea victoria* green fluorescent protein, or a mutant *Aequorea victoria* green fluorescent protein.

32. The method according to claim 30, wherein said transmembrane potential change detection system is a FRET-based assay.

33. The method according to claim 30, wherein said ion sensitive detection system comprises an ion sensitive fluorophore selected from an UV light-excitable calcium indicator, a low affinity calcium indicator, a visible light-excitable calcium indicator, an UV light-excitable magnesium indicator, or a visible light-excitable magnesium indicator.

34. The method according to claim 29, wherein said polypeptide comprises a zinc finger DNA binding domain that is heterologous to said target gene.

35. The method according to claim 29, wherein said polypeptide comprises DNA binding domain that is heterologous to said target gene and is selected from a nuclear receptor DNA binding domain, a Gal4 DNA binding domain or a LexA DNA binding domain.

36. The method according to claim 29, wherein said target gene is selected from a nuclear receptor, a G-protein subunit, an ion channel subunit or a G-protein coupled receptor.

37. An isolated DNA construct comprising a promoter operatively linked to a DNA sequence which encodes a targeting sequence and a modulator domain, wherein:

a. each of said promoter, targeting sequence and modulator domain are heterologous to one another;

b. said targeting sequence comprises a region of homology to an endogenous target gene sufficient to promote homologous recombination of said DNA construct; and

c. said modulator domain is positioned in said DNA construct with respect to said targeting sequence, such that following said homologous recombination said promoter controls transcription of an mRNA encoding a polypeptide comprising an activatable domain and a modulator domain.

38. The DNA construct according to claim 37, wherein said modulator domain comprises a zinc finger DNA binding domain.

39. The DNA construct according to claim 37, wherein said modulator domain comprises a DNA binding domain selected from a nuclear receptor DNA binding domain, a Gal4 DNA binding domain or a LexA DNA binding domain.

40. The DNA construct according to claim 37, wherein said target gene is selected from a nuclear receptor, a G-protein subunit, an ion channel subunit or a G-protein coupled receptor.

41. The DNA construct according to claim 37, further comprising a selectable marker gene.

42. A recombinant cell line designated as HEK-293 MC4 c49 P4 ACD#12591 with ATCC Accession No. 5409.

43. A recombinant cell line designated as HEK-293 PPAR γ c4G5 P9 ACD#13607 with ATCC Accession No. 5405.

44. A recombinant cell line designated as HEK-293 GR c2F8 P5 ACD#13609 with ATCC Accession No. 5407.

45. A recombinant cell line designated as HEK-293 MR c1B4 P5 ACD#13687 with ATCC Accession No. 5408.

46. A recombinant cell line designated as HEK-293 Nurr1 c1E10 P7 ACD#13608 with ATCC Accession No. 5406.